DOING PHYSICS WITH PYTHON

A MINIMAL MODEL FOR TUMOR GROWTH AND CHEMOTHERAPY

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ns25TumorGrowth.py time evolution of N, T, I and C

ns25TumorGrowthG.py bifurcation diagrams

INTRODUCTION

A mathematical model is presented for the dynamics between tumor cells, normal cells, immune cells, and chemotherapy drug concentration. The immune system is designed to detect and kill anomalous cells. When this system fails, it results in an uncontrolled growth of the tumor cells and so it may be necessary for chemotherapy treatment. This minimal model of tumor growth considers both the immune response and chemotherapy treatment.

A tumor’s response to treatment depends on many factors, including the severity of the disease, the application of the treatment, and the strength of patient’s own immune response. Mathematical models of tumor growth can be a powerful tool to provide insights into the dynamics of tumor growth and treatment through the administration of drugs. Such models can play a significant role in the development of a better understanding of cancer diseases and various drug therapy strategies to fight the disease.

Tumor cells are abnormal cells that divide and grow uncontrollably, potentially forming lumps or growths called tumors. These tumors can be benign (non-cancerous) and generally do not spread to other parts of the body or malignant (cancerous) that can invade nearby tissues and spread (metastasis).

Immune cells (white blood cells or leukocytes) are the body's defence system against infection and disease. They are produced in the bone marrow and circulate throughout the body in the blood and lymphatic system. These cells identify and eliminate harmful pathogens like bacteria, viruses, fungi, and cancerous cells.

Chemotherapy kills cells through a mass-action dynamic where mass-action dynamics refers to the principle that the rate of a change is directly proportional to the product of the populations or concentrations of the reacting substances.

Through the construction and analysis of mathematical models, researchers can explore the complex interplay among tumor cells, normal cells, immune cells, and the surrounding microenvironment. This can give an insight into the factors that drive tumor initiation, growth, invasion, and treatment resistance. By quantifying these interactions, dynamical system models offer a foundation for developing targeted and effective therapeutic strategies.

MINIMAL MODEL

The minimal model proposed describes three types of cells and one drug concentration:

- $N(t)$ **N**ormal cell population (normalized $N(0) = 1$)
- $T(t)$ **T**umor cell population
- $I(t)$ **I**mmune cell population
- $C(t)$ **C**hemotherapy drug concentration (amount of drug at tumor site at time t)

Four non-linear ordinary differential equations are used to represent the time rate of change of each of these four variables.

The model's assumptions used to determine the equations are:

1. Both tumor and normal cell populations are homogeneous (their growth dynamics are the same for all parts of the population)

where tumor, and normal cell populations obey logistic dynamics.

2. Immune cells are produced at a constant rate, and have a death rate proportional to the number of immune cells.
3. Tumor cells, immune cells, and normal cells all compete with each other for available resources through mass-action dynamics in a predator-prey fashion.
4. It is assumed that the drug is delivered by infusion, and there is an instantaneous mixing of drug with plasma, as well as an immediate delivery of the drug to the tumor site. The drug kills tumor cells, immune cells, and normal cells through mas-action dynamics.

The four rates of change equations are solved numerically using the Python function odeint.

$$\dot{N} = r_2 N\left(1-\frac{N}{K_2}\right) - c_4 T N - a_3 C N \tag{1}$$

$$\dot{T} = r_1 T\left(1-\frac{T}{K_1}\right) - c_2 I T - c_3 T N - a_2 C T \tag{2}$$

$$\dot{I} = s + \frac{k_1 I T}{k_2 + T} - c_1 I T - d_1 I - a_1 C I \tag{3}$$

$$\dot{C} = k_3 V - d_2 C \tag{4}$$

Units for $N(t)$, $T(t)$, $I(t)$ are cells, time t in days and $C(t)$ is a dimensionless quantity for the drug concentration and its toxicity.

The default model parameters are summarised in Table 1.

Table 1. Default parameter values

$r_2 = 1.00$ day^{-1} $r_1 = 1.50$ day^{-1}

$K_1 = 1.00$ cell $K_2 = 1.00$ cell

$a_1 = 0.20$ day^{-1} $a_2 = 0.30$ day^{-1} $a_3 = 0.10$ day^{-1}

$c_1 = 1.00$ cell^{-1}.day^{-1} $c_2 = 0.5$ cell^{-1}.day^{-1}

$c_3 = 1.00$ cell^{-1}.day^{-1} $c_4 = 1.00$ cell^{-1}.day^{-1}

$d_1 = 0.20$ day^{-1} $d_2 = 1.00$ day^{-1}

$k_1 = 0.01$ day^{-1} compromised immune system $(0.01 < k_1 < 2)$

$k_2 = 0.30$ cell

$k_3 = 1.00$ day^{-1}

$s = 0.33$ cell.day^{-1} $(0 < s < 0.5)$

The units for cells are scaled, so that one unit represents the maximum normal cell population in the region of the tumor. A reasonable approximation is that the tumor site contains in the order of 10^{11} cells. Therefore, a scaled population $x = 1$ and contains 10^{11} cells.

If one assumes that there about $5\text{x}10^8$ cells.cm^{-3} of tissue at the tumor site, then the volume and diameter for a scaled population x are

$$\text{volume} = x\left(10^{11} / 5\times 10^{8}\right) = 200\,x \text{ cm}^3$$

$$\text{diameter} = 2\left(\frac{(3)(200x)}{4\pi}\right)^{1/3} = 7.3\,x^{1/3} \text{ cm}$$

Thus, when the normal cell population at carrying capacity is $K_2 = 1$ ($N = 1$) the number of cells is 10^{11}, the spherical volume of tissue encompassing the normal cells is about 200 mL and the corresponding diameter is about 7.3 cm.

The clinical detection threshold for a tumor is generally 10^7 cells. Hence the scaled tumor population, its volume, and diameter are

$T = 10^{-4}$ volume = 0.02 cm^3 diameter = 0.34 cm

In a simulation with $T(0) = 0.25$, then $x = 0.25$, the number of cells is 0.25×10^{11} and its volume is 50 cm^3 and diameter is 4 cm which is well above clinical detection levels.

The growth of the normal and tumor populations is represented by a logistic equation

normal cells $\dot{N} = r_2 N\left(1 - \frac{N}{K_2}\right)$ tumor cells $\dot{T} = r_1 T\left(1 - \frac{x_1}{K_1}\right)$

where r_2 is the normal cell growth rate, K_2 the normal cell carrying capacity, r_1 the tumor cell growth rate and K_1 the tumor cell carrying capacity (figure 1). The normal growth rate r_2 is normalized ($r_2 = 1$). The carrying capacity places a limit on the maximum size of a population. For example, if $K_1 = 1$ then tumor diameter is about 7.3 cm and if $K_1 = 2$ then tumor diameter is 9.2 cm.

The logistic equation is a mathematical model that describes how a population grows when resources are limited. The logistic equation results in a growth curve, where the population initially grows or decreases exponentially, then slows down as it approaches the carrying capacity, eventually stabilizing around that limit.

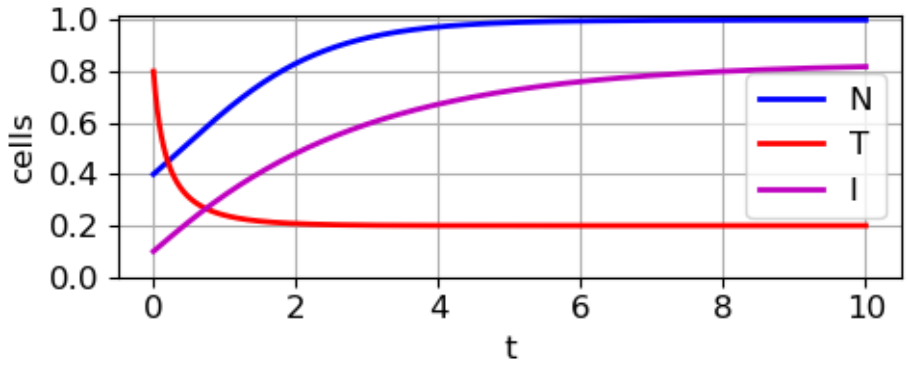


Fig. 1. Logistic growth of the normal and tumor cell populations where K_1= 0.2 (Tumor) and K_2 = 1.0 (Normal) with initial populations $N(0) = 0.4$, $T(0) = 0.8$ and $I(0) = 0.1$. Growth rates $r_1 = 1.50$ and $r_2 = 1.00$. The populations evolve to the carrying capacities K_1 and K_2.

Cells are killed by chemotherapy through mass-action dynamics:

Normal cells are killed by chemotherapy $-a_3\, C\, N$

Tumor cells are killed by chemotherapy $-a_2\, C\, T$

Immune cells are killed by chemotherapy $-a_1\, C\, I$

$0 \le a_i \le 0.50 \qquad a_3 \le a_1 \le a_2$

The value 0.50 gives an upper bound on the efficiency of a drug in killing cells.

Competition terms c_1, c_2, c_3, c_4 mass-action dynamics:

Cells destructively competing with each other for resources and space

Death of normal cells by tumor cells $-c_4 T N$

Death of tumor cells by normal cells $-c_3 T N$

Death of tumor cells by immune cells $-c_2 I T$

Death of immune cells by tumor cells $-c_1 I T$

Death rates d_1, d_2

Death rate of immune cells d_1 Death rate of drug d_2

Immune source rate s

Constant source rate for production of immune cells (constant influx of immune cells into tumor site) $0 \le s \le 0.50$.

Immune response rate k_1 and immune threshold rate k_2

$$\frac{k_1 x_1 x_2}{k_2 + x_1}$$

Immune cells are recruited by tumor cells that leads to a saturation effect. The presence of tumor cells stimulates the immune response, represented by the positive nonlinear growth term for the immune cells. However, the immune system response may not be sufficient on its own to completely combat the rapid growth of the tumor cell population and the eventual development into a tumor.

The rate to deliver the drug is denoted by the dimensionless variable $V(t)$. A goal using drug therapy is to use the optimal drug

administration that destroy the tumor cells, and to restore the normal cell population with minimal harm to a patient.

SIMULATIONS

1. Zero tumor cells and zero chemotherapy

In the absence of any tumor cells $T(t) = 0$, and drug treatment $C(t) = 0$, then, there is a balance between the influx of immune cells, ($s = 0.33$) and their deaths ($d_1 = 0.20$), resulting in a long-term immune population size of $s/d_1 = 1.65$ cells.

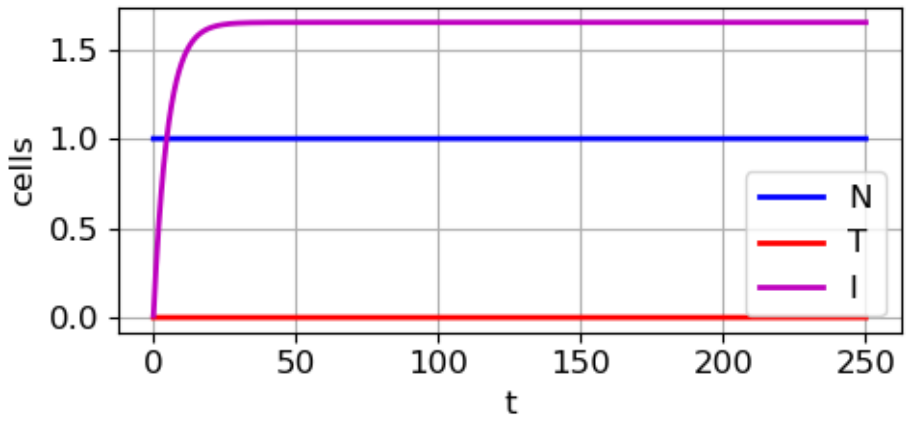


Fig. 2. Time evolution of cell populations for zero tumor cells and zero chemotherapy. $\dot{I} = s - d_1 I_{ss} = 0 \Rightarrow I_{ss} = s/d_2 = 1.65$

N(0) = 1.00 T(0) = 0.00 I(0) = 0.10 C(0) = 0.00

Nf = 1.00 Tf = 0.00 If = 1.65

volN = 200.00 volT = 0.00 volI = 330.00

diaN = 7.26 diaT = 0.00 diaI = 8.57

volumes in mL and **dia**meters in cm

2. Presence of tumor cells stimulates the immune response

For zero chemotherapy, the presence of tumor cells stimulates the immune response represented by the positive nonlinear growth term $+k_1 I T / (k_2 + T)$ and competition between normal cells, tumor cells and immune cells lead to the death or inactivation of cells.

With an initially small tumor cell population $T(0) = 0.14$, then the presence of these tumor cells can stimulate the growth of the immune cells that results in the complete destruction of all tumor cells. So, in this instance, the immune response can destroy the tumor.

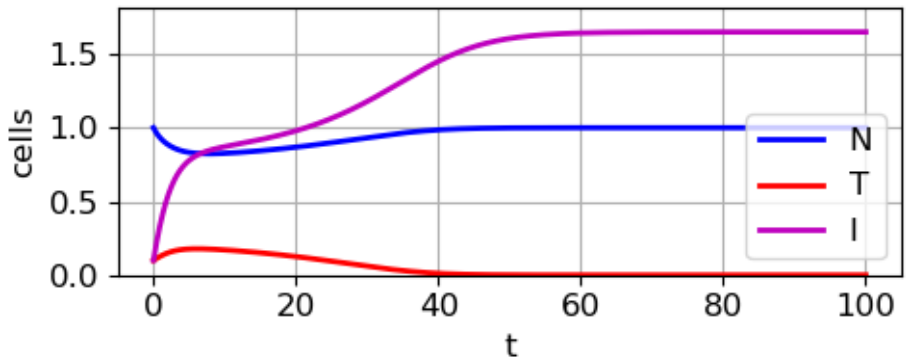


Fig. 3. $N(0) = 1.00$, $\boldsymbol{T(0) = 0.14}$, $I(0) = 0.10$.

An initial small tumor cell population will stimulate the production of immune cells resulting in the complete destruction of the tumor. All three cell populations converge to their steady-state vales

$N_{ss} = 1.00$, $T_{ss} = 0$, $I_{ss} = 1.65$, tumor diameter = 0.

However, it is a completely different story if there is a slightly higher initial tumor cell population. No longer is the tumor destroyed by the immune cell response. There is a critical initial tumor population $T_C \sim 0.14$. For an initial tumor cell population $T(0) > T_C$, then all three populations will converge to their steady-state values $T_{ss} = 0.56 > I_{ss} = 0.44 \approx N_{ss} = 0.44$ as shown in figure 4. Thus, when $T(0) > T_C$ a tumor will develop with more tumor cells than normal cells and insufficient number of immune cells to kill the tumor cells with steady-state cell populations independent of the initial tumor cell population provided $T(0) > T_C$ (figures 4A and 4B).

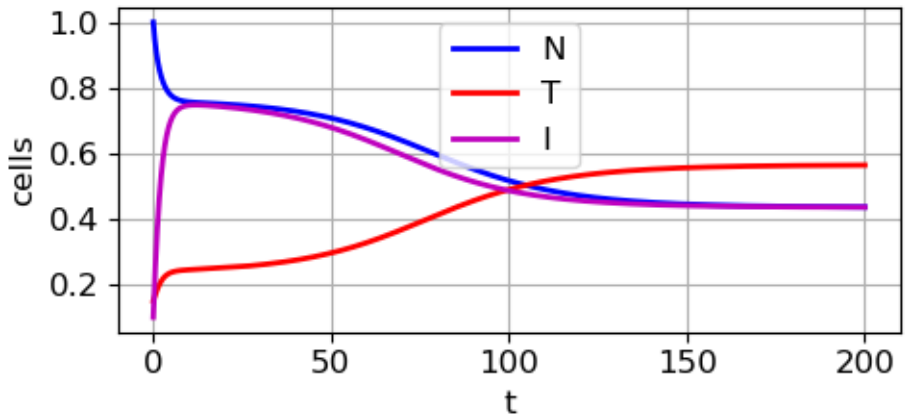


Fig. 4A. $N(0) = 1.00$, $\boldsymbol{T(0) = 0.15}$, $I(0) = 0.10$.

Tumor not destroyed

$N_{ss} = 0.44$, $T_{ss} = 0.56$, $I_{ss} = 0.44$

Tumor diameter $\approx$ 6.0 cm

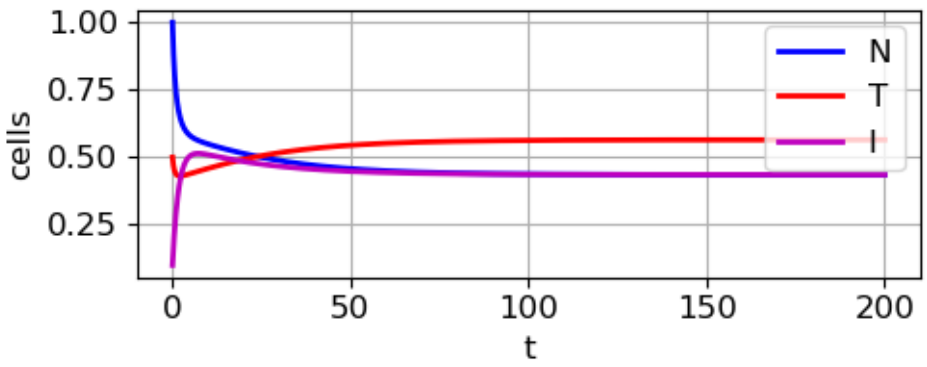
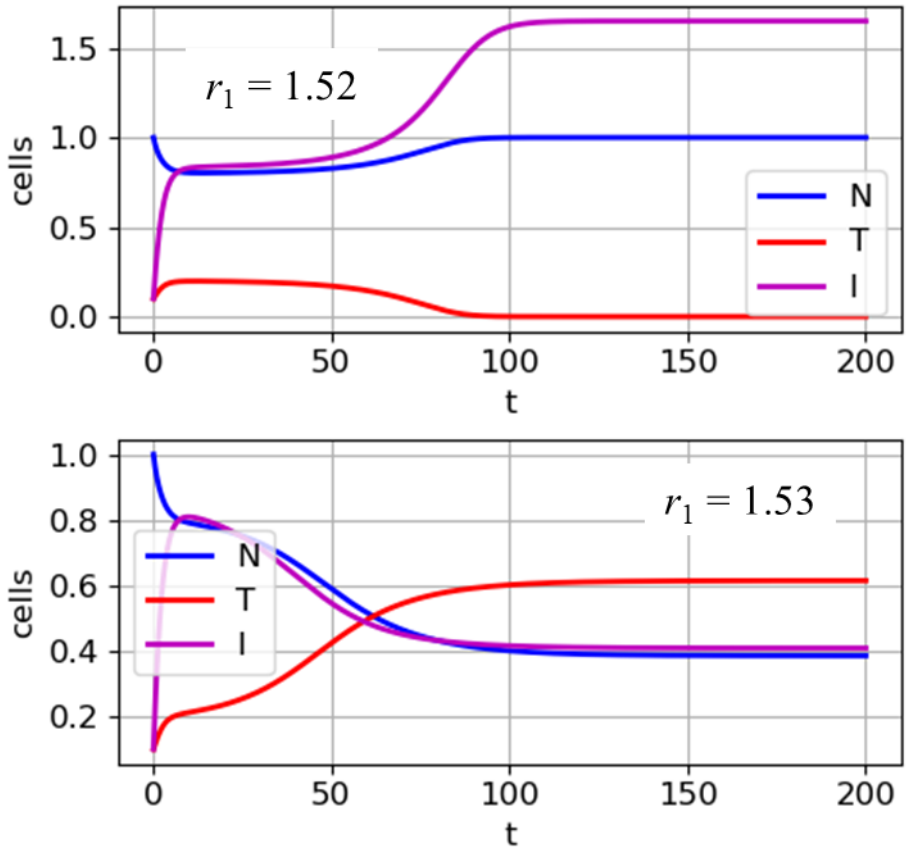


Fig. 4B. Tumor not destroyed
$N(0) = 1.00$, $\boldsymbol{T(0) = 0.50}$, $I(0) = 0.10$.
$N_{ss} = 0.44$, $T_{ss} = 0.56$, $I_{ss} = 0.44$
Tumor diameter ≈ 6.0 cm

If the initial tumor population is greater than a critical value $T_C \sim 0.14$, then the tumor is not destroyed and all three cell populations converge to their steady-state values. The steady-state values are independent of the initial tumor cell population when $T(0) > T_C$

3. Evolution of cell populations dependence on tumor growth rate

In the absence of any chemotherapy treatment, whether a tumor is destroyed or persists is very dependent on the growth rate of the tumor cells, r_1. A more aggressive tumor will have a higher growth rate and can result in the formation of a tumor. The critical value for the tumor growth rate is $r_{1C} \sim 1.52$. For $r_1 < r_{1C}$ or $r_1 > r_{1C}$ there is a dramatic difference in the response of the system (figure 5).



Fig, 5. $T(0) = I(0) = 0.1$. For the larger growth rate (1.53 > 1.52), a tumor is created as the immune response is insufficient to destroy all the tumor cells.

$r_1 = 1.52$ $T_{ss} = 0$ $I_{ss} = 1.65$ $N_{ss} = 1.00$

$r_1 = 1.53$ $T_{ss} = 0.61$ $I_{ss} = 0.44$ $N_{ss} = 0.39$.

For very aggressive tumors (large r_1 values $r_1 >> r_C$), then the steady-state normal cell population becomes very small $N_{ss} \sim 0$.

A person's immune response in very important in determining whether a cancer will continue to grow. The parameter c_2 is the proportionality constant for the immune cells killing the tumor cells. When the immune cells are less effective in killing tumor cells, it may result in the existence of tumor cells and a reduced normal cell

population. The system's response is very sensitive to the value of this parameter c_2. The fixed point for the steady-state population N_{ss} = 1.0 shown in figure 6 is unstable. The parameters for figure 6A are r_1 = 1.50 and c_2 = 0.48. Figure 6B shows the cell population when c_2 = 0.47 where N_{ss} = 0.38. For c_2 = 0.47 the tumor cell population grow to its steady-state value, the immune cell population peaks then falls to its steady-state value, and the normal cell population declines to its steady-state value.

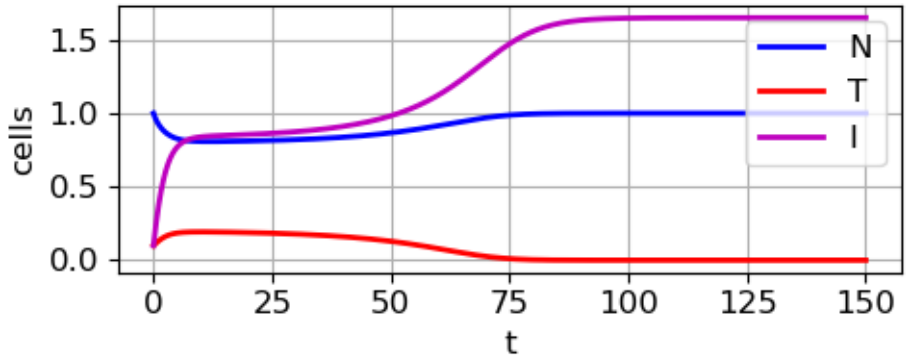


Fig. 6A. $\boldsymbol{c_2 = 0.48}$. Immune cells are effective in killing are the tumor cells. N_{ss} = 1.00 T_{ss} = 0 I_{ss} = 1.65 C_{ss} = 0.00

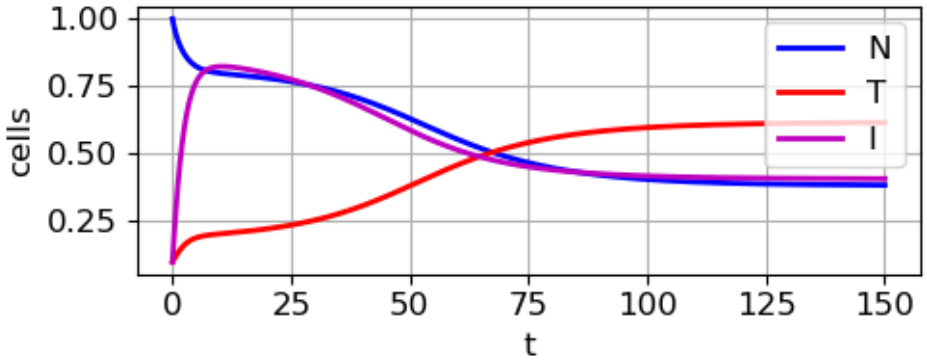


Fig. 6B. $\boldsymbol{c_2 = 0.47}$. Immune cells do not kill all tumor cells. At equilibrium there are more tumor cells than normal cells. The tumor diameter has increased from 3.4 cm to 6.2 cm.
N_{ss} = 0.38 T_{ss} = 0.62 I_{ss} = 0.41 C_{ss} = 0.00

4. CHEMOTHERAPY

We have seen that a tumor will develop if the initial cell population or its growth rate exceed their critical values. In such cases, the immune response if insufficient in destroying the tumor. So, it may be necessary to administer chemotherapy to such cancer patients. The minimal model can simulate the administration of the drug through the variable V in equation 4 for the drug concentration.

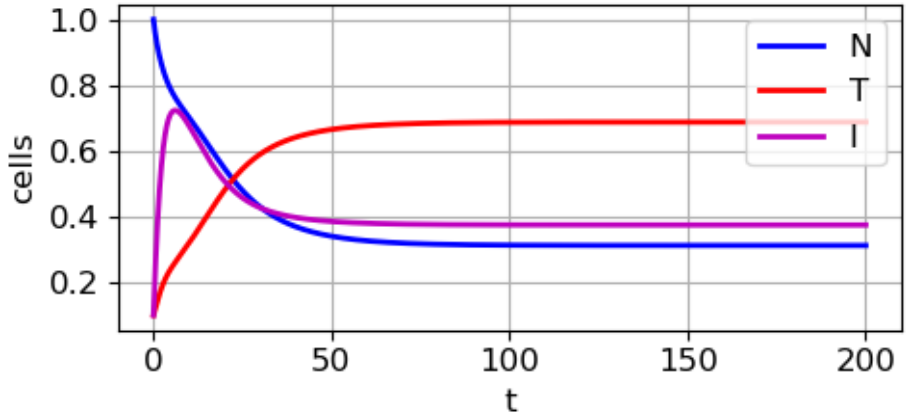


Fig. 7. $\boldsymbol{V(t) = 0}$, $\boldsymbol{r_1 = 1.6}$, $N(0) = 1.00$, $T(0) = 0.1$, $I(0) = 0.1$.
No drug treatment. The cell populations N, T and I converge to their steady-state values where $T_{ss} > I_{ss} > N_{ss}$. A tumor exists and there is a decline in the normal cell population from its initial value.

$r_1 = 1.60 \quad T_{ss} = 0 \quad I_{ss} = 0.37 \quad N_{ss} = 0.31$

When the drug is given for 10 days (20 to 30) with concentration $V = 3.30$, the drug strength and duration is not sufficient to kill all the tumors and as a result the three populations converge to their steady-state values. However, the slight the increase in the initial value of V to $V(0) = 3.40$ will result in the destruction of the tumor (figure 8).

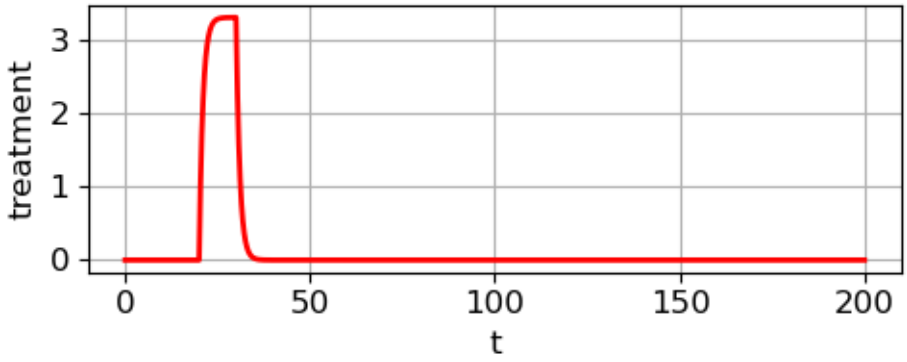


Fig. 8A. Drug concentration administered for 10 days (20 to 30 days) Drug delivered = 33 units where the drug delivered is equal to the area under the curve.

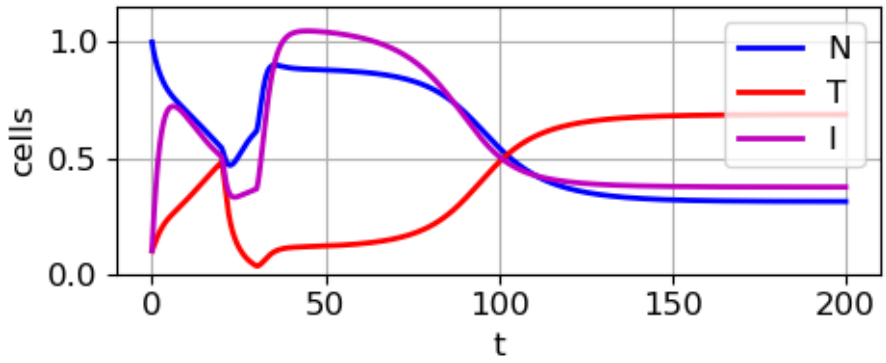


Fig. 8B. The drug delivery is insufficient to destroy the tumor.
***V*(*t*) = 3.30 *dt* = 10** Drug delivered = 33 units
$r_1 = 1.60$ $T_{ss} = 0.69$ $I_{ss} = 0.37$ $N_{ss} = 0.31$

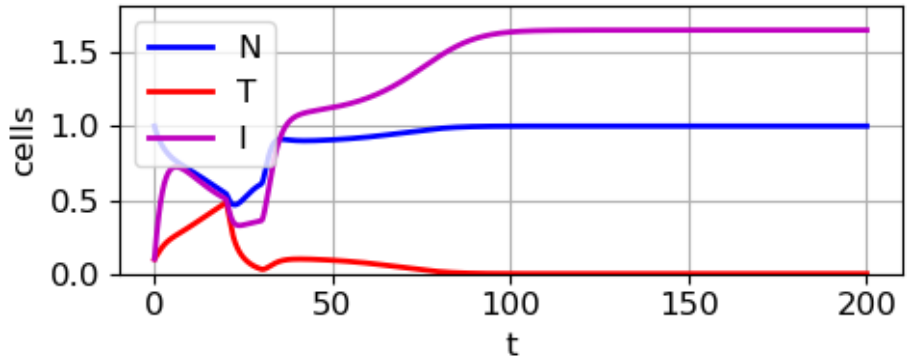


Fig. 8C. The drug delivery destroys the tumor.
***V*(*t*) = 3.40 *dt* = 10** Drug delivered = 34 units
$r_1 = 1.60$ $T_{ss} = 0$ $I_{ss} = 1.65$ $N_{ss} = 1.00$

For the case when $V(t) = 3.30$ and duration of 10 days results in a tumor. But if the duration is increased by one day (**11** days) then the tumor will be destroyed.

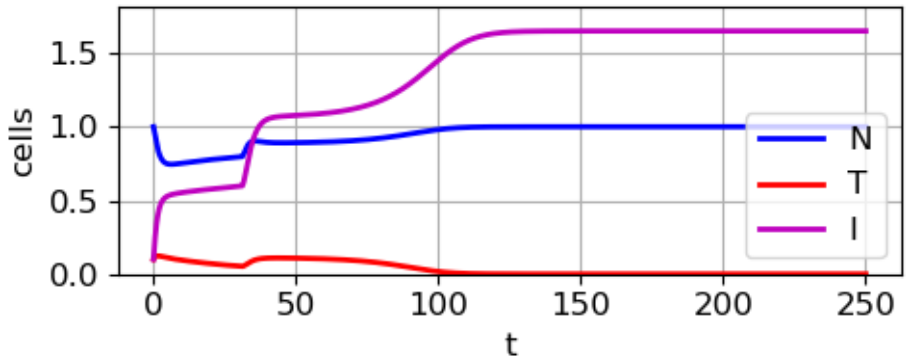


Fig. 8D. The drug delivery destroys the tumor.

$\boldsymbol{V(t) = 1.504 \quad dt = 11}$ Drug delivered = 36 units

$r_1 = 1.60 \quad T_{ss} = 0 \quad I_{ss} = 1.65 \quad N_{ss} = 1.00$

Again, we see that a small increment in a control parameter may result in a very different response of the system.

In the treatment of a cancer, it is best to use the smallest amount of a drug to kill all the tumor cells and to protect the normal cells and reduce any side effects. One may think of using a small dose of the drug given for repeated short periods of time. But this approach is not necessarily successful. Consider the case when a drug is given for 5 days and then zero drug for 5 days and this sequence done four times $(V_0 = 2.90,\ dt = 5)$ as shown in figure 9. This strategy is not successful in killing all the tumor cells. By comparing figure 9 with

figure 8, we can conclude that a single dose of appropriate concentration and duration is more successful in destroying the tumor than the repeated dose given in short time intervals. During the administration the number of tumor cells decreases. But as soon as the administration of the drug is stopped, the tumor cell numbers again increase.

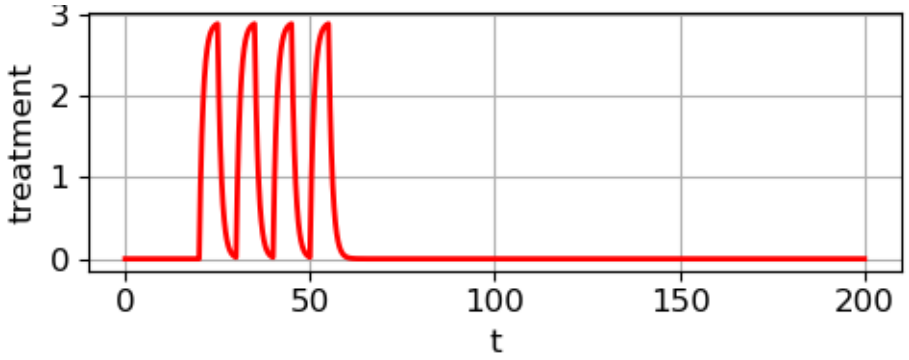


Fig. 9A. Drug delivered = 58 units.
Drug administered four times: $V = 2.90$ for 5 day and no drug $V = 0$ for five days.

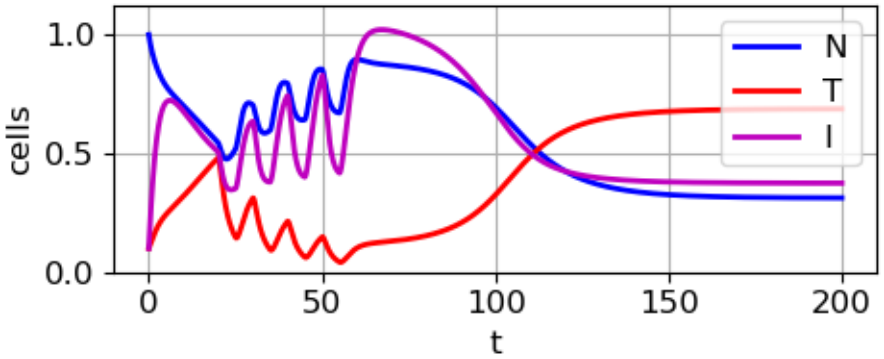


Fig. 9B. Tumor not destroyed. Drug delivered = 58 units.

Short bursts of lower concentration drug administered does not kill the tumor cells, even though the amount of drug delivered is 58 units compared with 36 units for the case shown in figure 8D.

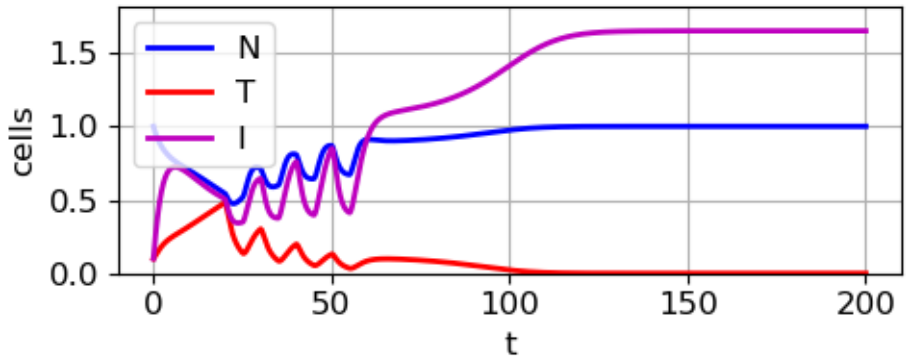


Fig. 9C. Tumor destroyed. Drug delivered = 60 units.

The amount of drug delivered that results in the killing of all the tumor cells is 60 units which is significantly higher than the single large administration of the drug of 36 units as shown in figure 8D.

The strategy of administering repeated small doses in short periods does not result in the destruction of the tumor. At first, cancerous cells started growing (growth period) and after drug delivery the number of tumor cells is reduced (death period) and at the end when the drug delivery is stopped tumor cells start growing again (dormancy period).

A standard protocol is to administer a drug for a short time, on the order of several hours with periodically repeated treatments every few weeks (pulsed chemotherapy). We see from the minimal model that this is not necessarily a reliable method for the system to evolve to be tumor free. In cases of a less aggressive tumor growth rate or a slightly stronger immune system, then chemotherapy treatment may

be sufficient to push the system to the desirable tumor-free equilibrium point. This means that even after the medicines are turned off, the tumor burden will continue to decrease toward zero. Otherwise, with more aggressive tumor growth or a weaken immune response then the system can be driven to the large tumor equilibrium point.

BIFURCATION DIAGRAMS

We can find the steady values for N, T, I, and C which correspond to fixed points by solving the set of equations 5, 6, 7, and 8. The steady-state values (fixed points) are N_{ss}, T_{ss}, I_{ss} and C_{ss}. The trivial case where the steady-state values are zero is ignored.

$$(5) \qquad r_2 N_{ss}\left(1-\frac{N_{ss}}{K_2}\right)-c_4 T_{ss} N_{ss}-a_3 C_{ss} N_{ss}=0$$

$$(6) \qquad r_1 T_{ss}\left(1-\frac{T_{ss}}{K_1}\right)-c_2 I_{ss} T_{ss}-c_3 T_{ss} N_{ss}-a_2 C_{ss} T_{ss}=0$$

$$(7) \qquad s+\frac{k_1 I_{ss} T_{ss}}{k_2+T_{ss}}-c_1 I_{ss} T_{ss}-d_1 I_{ss}-a_1 C_{ss} I_{ss}=0$$

$$(8) \qquad k_3 V-d_2 C_{ss}=0 \quad \Rightarrow C_{ss}=k_3/d_2$$

We want to find the dependence of the steady-state values as a function of a control variable such as r_1. Solving this set of equations algebraically is difficult because at a bifurcation point, a dramatic change occurs in the steady-state values for a small increment in the

control parameter. To overcome this problem, the ODEs for the system are solved for the time evolution of the normal, tumor and immune cells. The time span is chosen large enough for the populations to reach their steady-state values. Then, the steady-state values are set equal to the last cell populations computed.

The time evolutions of the cell populations are very dependent on the magnitude of the tumor cell growth rate, r_1. Figure 10 shows the bifurcation diagram for the tumor cell growth rate, r_1 which there is no chemotherapy treatment.

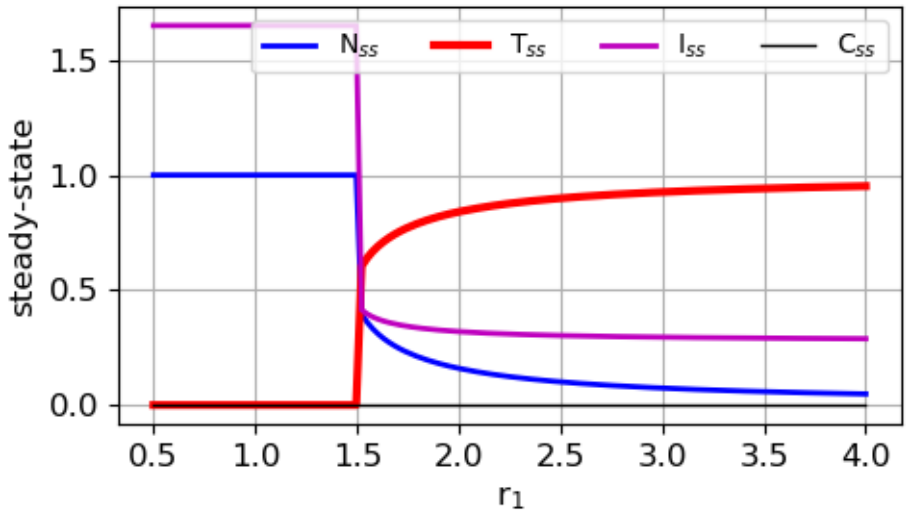


Fig. 10. Bifurcation diagram for the tumor cell growth rate, r_1. No chemotherapy treatment $V(t) = 0$.

The bifurcation point is $r_1 \sim 1.52$. For growth rates greater then 1.52, then the steady-tumor cell population becomes greater than either of the normal cell or immune cell populations

$$r_1 \to \infty \quad N_{ss} \to 0 \quad T_{ss} \to 1 \quad I_{ss} \to 0.30$$

For $r_1 > \sim 1.52$ the immune response is insufficient in controlling the growth of the tumor and protecting the normal cells.

The tumor can be treated with chemotherapy. The success of the treatment depends on the tumor growth rate and the magnitude and duration of the chemotherapy treatment as shown in figure 11. The bifurcation point r_C increases with the magnitude of the drug concentration or a longer administration time interval. For growth rates near the bifurcation point r_C the success of destroying tumor is very sensitive to the magnitude of the drug concentration and administration time. As shown in figure 11, the tumor is either destroyed and the normal cell population protected, or the tumor cells dominate and the normal and immune cell populations evolve to small populations.

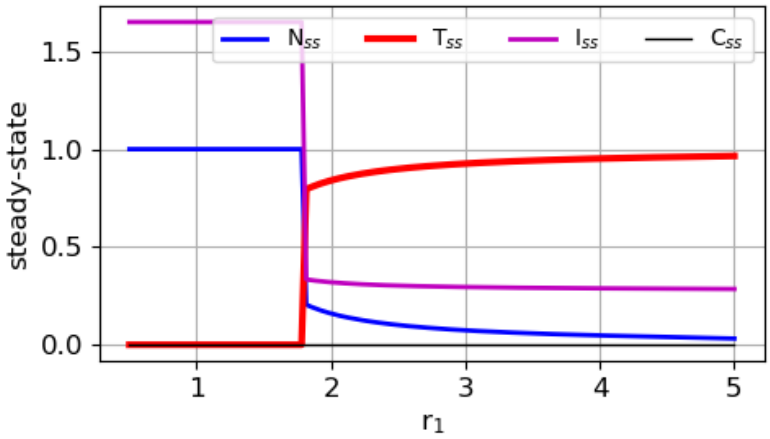


Fig. 11A. $V = 4.00$, $dt = 10$ (20-30 days) $r_C \sim 1.80$.

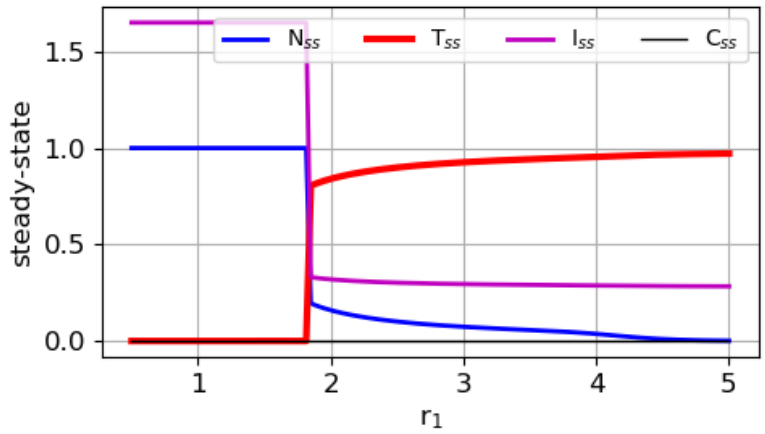


Fig. 11B. $V = 4.00$, $dt = 40$ (20-60 days) $r_C \sim 1.85$.

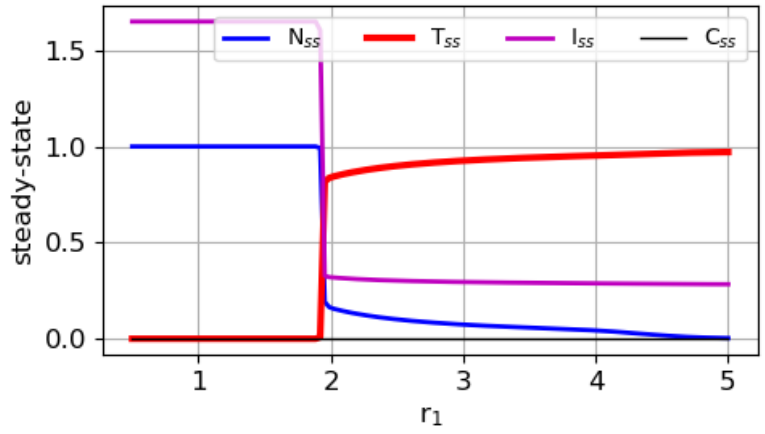


Fig. 11C. $V = 8.00$, $dt = 10$ (20-30 days) $r_C \sim 1.95$.

How effective the immune cells are in killing tumor cells is governed by the parameter c_2 in equation 2 for the rate of change of the tumor population $\left(-c_2 I T\right)$. Figure 12 shows the bifurcation diagram for the steady-state normal, tumor and immune cell populations as a function of the immune parameter c_2.

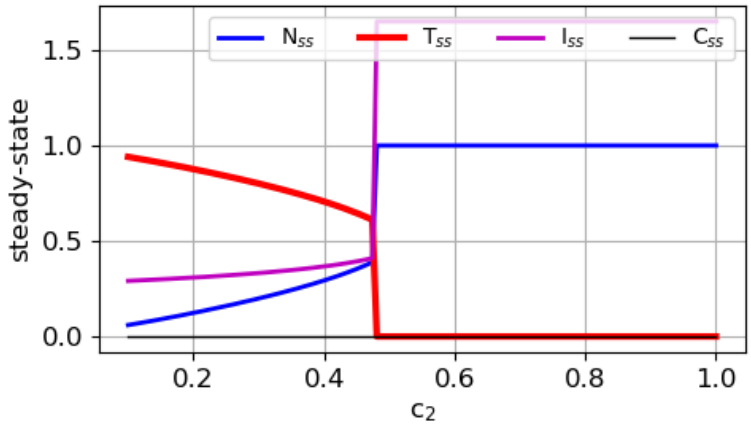


Fig. 12A. Steady-state response of the system as a function of the immune parameter c_2 for zero chemotherapy. The bifurcation value of c_2 is ~0.48.

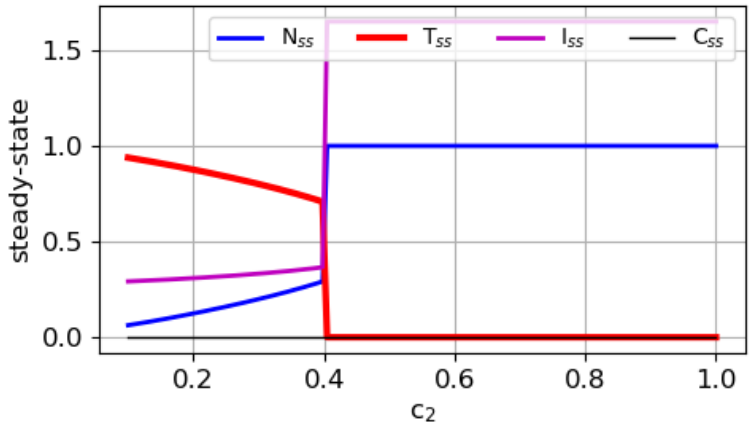


Fig. 12B. Steady-state response of the system as a function of the immune parameter c_2 with chemotherapy $\left(20 < t < 60 \;\; V = 1 \text{ otherwise } \; V = 0\right)$. The bifurcation value of c_2 is ~0.40 which is lower than the case for zero chemotherapy.

CONCLUSIONS

The minimal model proposed can be used effectively for studying the behaviour of cancerous cells in presence of chemotherapy. Graphical representation rather than algebraic means is one of the features of the minimal model. Whether a tumor is destroyed or not can be investigated by changing any of the model's constants many of which act as bifurcation parameters. Changes in the magnitude and time sequence of administering the drug is of parament importance in determining if the tumor cells are destroyed or multiple. There is a possibility that the minimal model may be used to find optimal and or better outcomes by modelling the administering medications in ways that have not been previously employed clinically. Mathematical modelling provides a theoretical framework to predict the long-term treatment outcomes, which is difficult to be realized by clinical studies.

The predictions of the model highlight the significance that a small change in a model parameter can have a dramatic effect upon the time evolution of the normal cell, tumor cell and immune cell populations. The model indicates that a short high intensity drug treatment may be superior in controlling a tumor than repeated low drug dose treatments and this strategy may deliver less drug in total to a patient.

REFERENCES

This minimal model is a modification of the models described in the two papers:

Ghaffari A., and Nasserifar, A. *Mathematical Modeling and Lyapunov-Based Drug Administration in Cancer Chemotherapy*
ns25TumorGrowthC.pdf

Depillis L.G., and Radunskaya A. *The Dynamics of an Optimally Controlled Tumor Model: A Case Study*
ns25TumorGrowthCC.pdf